Armed Forces College of Medicine

AFCM

Folic acid and neural tube defects

By

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Lecture Key points

1. The functions of folic acid
2. Clinical disorders of folic acid deficiency and neural tube defects
3. Folate analogues and their clinical applications in Medicine

INTENDED LEARNING OBJECTIVES (ILO)

By the end of this lecture the student will be able to:

1. **Distinguish the active form and functions of folic acid**
2. **Correlate folic acid deficiency to it clinical disorders and neural tube defects**
3. **Discuss folate analogues and their clinical applications in Medicine**

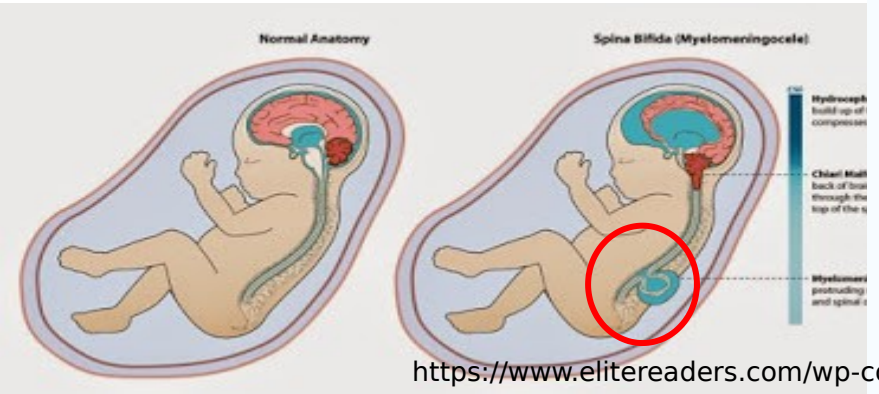
Case scenario

A30 years old woman pregnant for the third time at first trimester (no living child) with history of both pregnancies affected by neural tube defects (NTD) presented at 8 weeks period of gestation.

In the first pregnancy patient ha… pregnant) spontaneously after one … delivered at a … …ver, no comm… second pregnancy, gross congenita… were detected in her baby. The parents did not consent for postmortem autopsy or chromosomal study.

What is the probable diagnosis?

At the third pregnancy the doctor advise her with adequate folate nutrition and daily folic acid supplementation to avoid NTD



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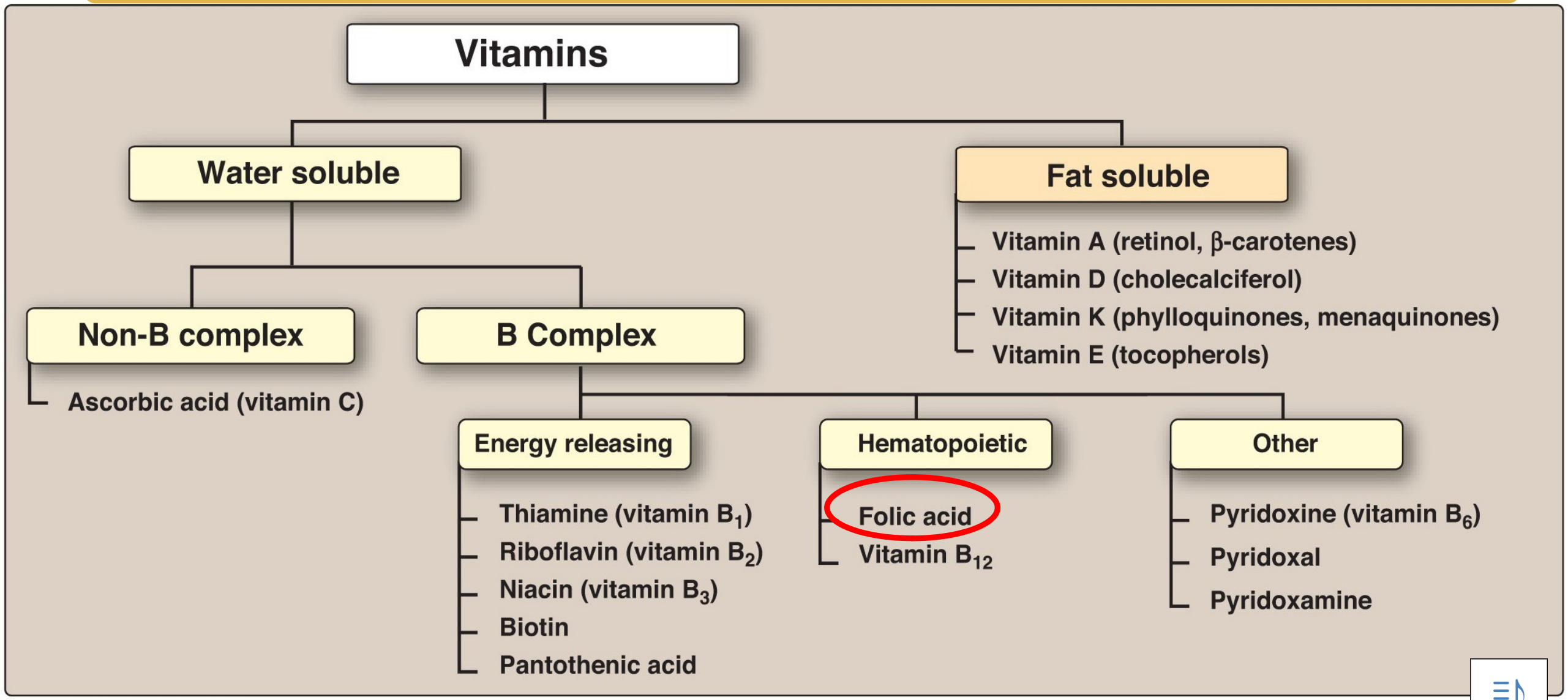
Classification of the vitamins



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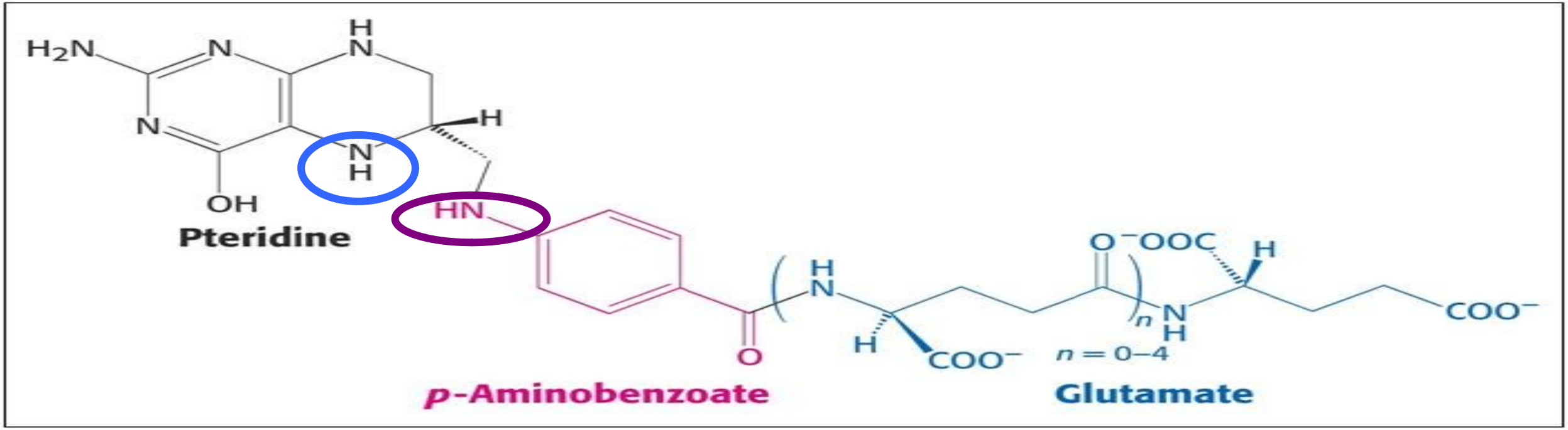
Structure of Folic Acid



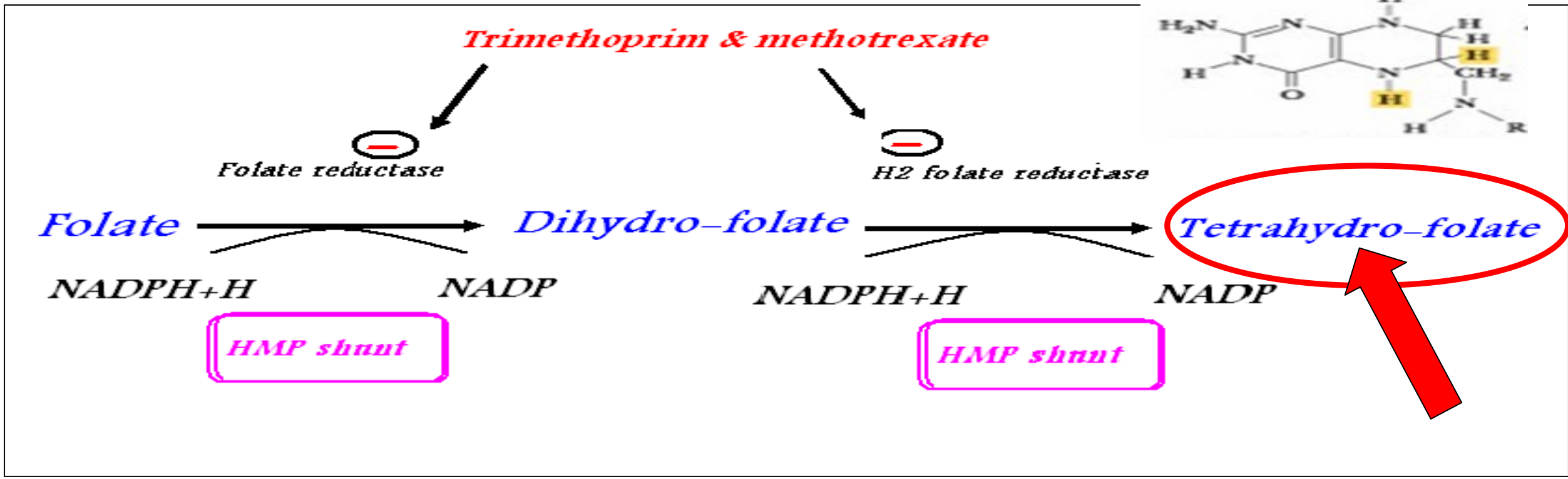
Human can not synthesis folic acid,

so it must supply in diet.

Folic acid (B9)

- **Human can not synthesis folic acid, so it must supply in diet**
- **Bacterial flora in intestine synthesizes folic acid**
- **Widely distributed in nature. It is abundant in green leafy vegetables, wheat, yeast and liver.**

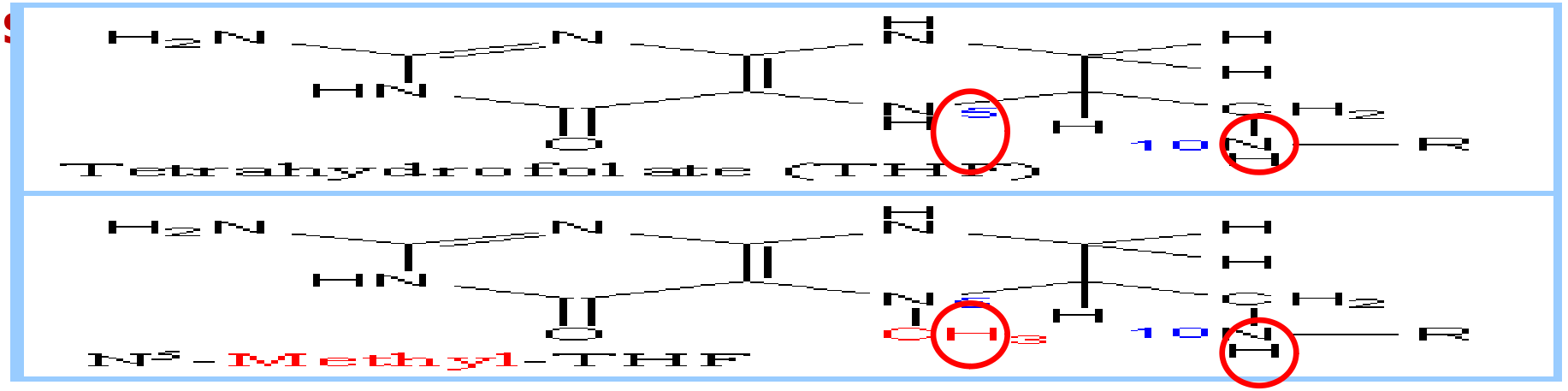
Activation of folate
Active form :tetrahydrofolic acid (THF)



Functions of THF

- **It acts as a carrier of one carbon groups Which carried on** either to ***N^5 or N^{10} nitrogen atom or to both***

- **one carbon group is important for purine (it provides C2 and C8 of purine ring) and the synthesis of deoxythymidine monophosphate (dTMP) of pyrimdine (DNA synthesis) and methionine (which is required for methylation reaction through SAM(S-Adenosyl methionine) especially in rapidly dividing cells e.g. developing WBCs, RBCs, platelets in bone marrow , surface epithelial cells of mouth, GIT, urinary tract, and respiratory tract and also growing fetus and in cancer cells**



One Carbon Metabolism

Definition:

It is the transfer of a single carbon unit from a donor to an acceptor

- **One carbon unit ranging from the fully oxidized form (CO2) to the fully reduced form methane (CH4).**

Types of one carbon unit:

1. **Methane (CH4)**
2. **Methyl group (-CH3)**
3. **Methylene group (-CH2-)**
4. **Methenyl group (-CH=)**
5. **Formyl group (-CH=O)**
6. **Formimino group (-CH=NH)**
7. **CO2 group**

Function of folic acid Quiz (USMLE)

Folic acid is important for which of the following processes?

A) Fatty acid oxidation

B) Fatty acid synthesis

C) Gluconeogenesis

D) One carbon metabolism

E) Glycogenesis

Causes of Folate deficiency

(1) Increase rate of cell division e.g. pregnancy, hemolytic anemia .

(2) Long term use of drugs:

oral contraception, estrogens, alcohol, and anticonvulsants (decrease absorption and increase catabolism of folate).

(3) Administration of methotrexate (inhibitor of dihydrofolate reductase) as anticancer chemotherapeutic.

(4) Alcholism

(5)poor absorption :caused due to defect in the small intestine.

(6) Mycotoxins (type of fungus) in contaminated corn meal

(7) Arsenic (Rat poision)

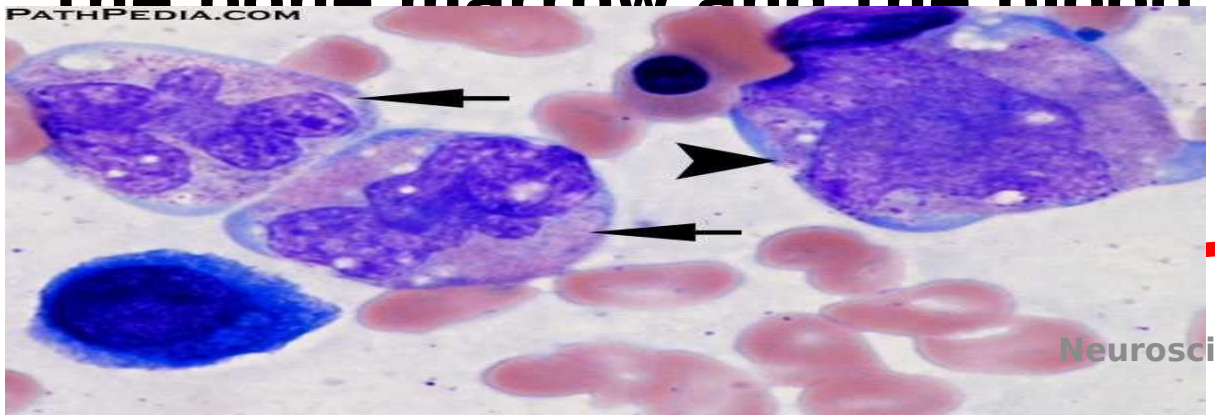
Manifestations of folate deficiency

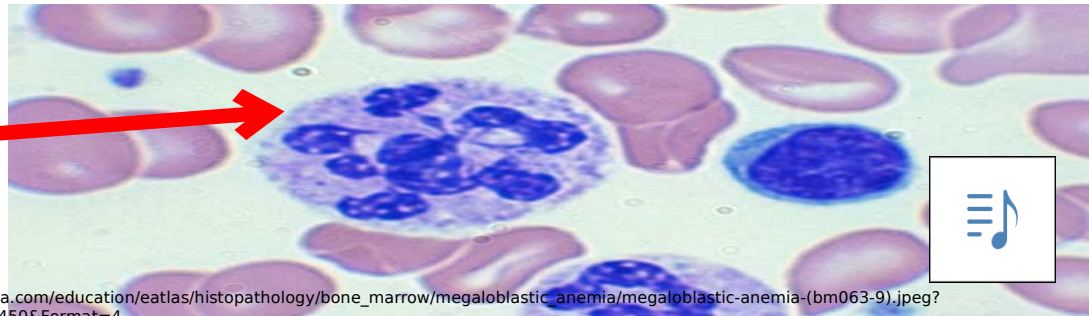
(1) Megaloblastic anemia (macrocytic hyperchromic anemia) or Leukopenia or thrombocytopenia or Pancytopenia:

As, the one carbon unit carried is required for synthesis of purines and pyrimidines

So, folate deficiency leads to inhibition of DNA synthesis which affects rapidly dividing cells as bone marrow cells (WBCs, RBCs, platelets).

It is called megaloblastic because there is accumulation of large, immature nucleated RBCs precursors, known as megaloblasts, in the bone marrow and the blood





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Explain on a biochemical basis?

(1) Megaloblastic anemia (macrocytic hyperchromic anemia) in folate deficiency

folate deficiency → **Inadequate serum levels of fola**

↓

No one carbon unit carried → **No synthesis of purines and pyrimidines (dTMP)**

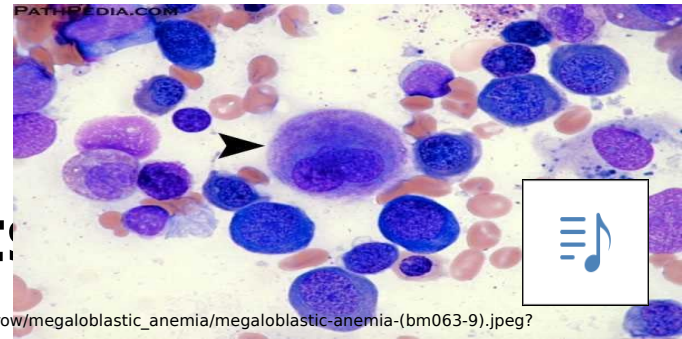
↓

Inhibition of DNA synthesis in rapidly dividing cells as bone marrow cells

↓

megaloblastic anemia

accumulation of megaloblast



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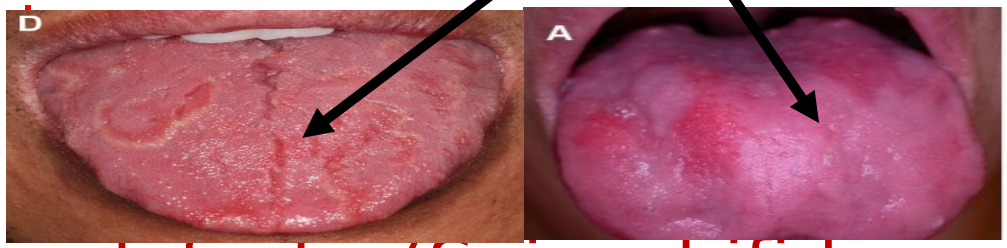
Manifestations of Folate deficiency

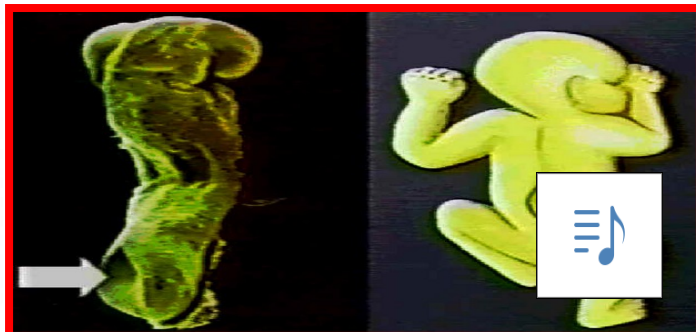
(2) Glossitis and gastrointestinal disturbances:

due to impaired DNA synthesis in GIT mucosal lining (rapidly dividing cells) as diarrhea & glossitis **(beefy red patch: diffuse bright erythema)**.



(3) Neural tube defects (Spina bifida and anencephaly) in the fetus:

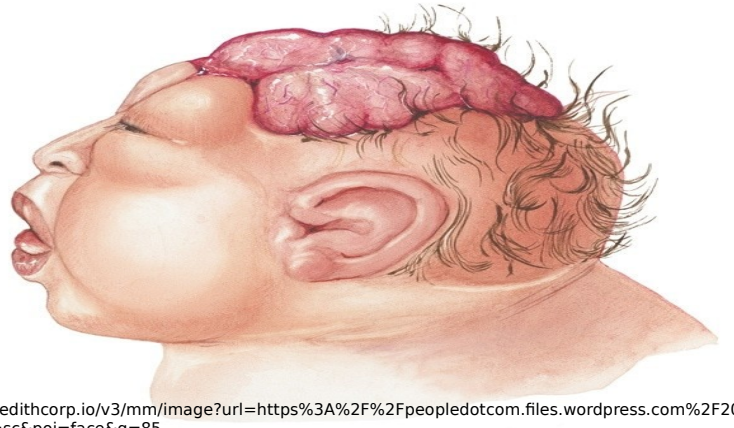
- occurs in the first week's pregnancy.
- Folic acid supplementation during the first trimester significantly reduces the defects.



Manifestations of Folate deficiency: Neural tube defects (NTD)

Neural tube defects

- are birth **defects** of the brain, spine, or spinal cord. They happen in the first month of pregnancy, often before a woman even knows that she is pregnant.
- The two most common **neural tube defects** are sp bifida and anencephaly) little to no brain)
- In spina bifida, the fetal spinal column doesn't close completely.



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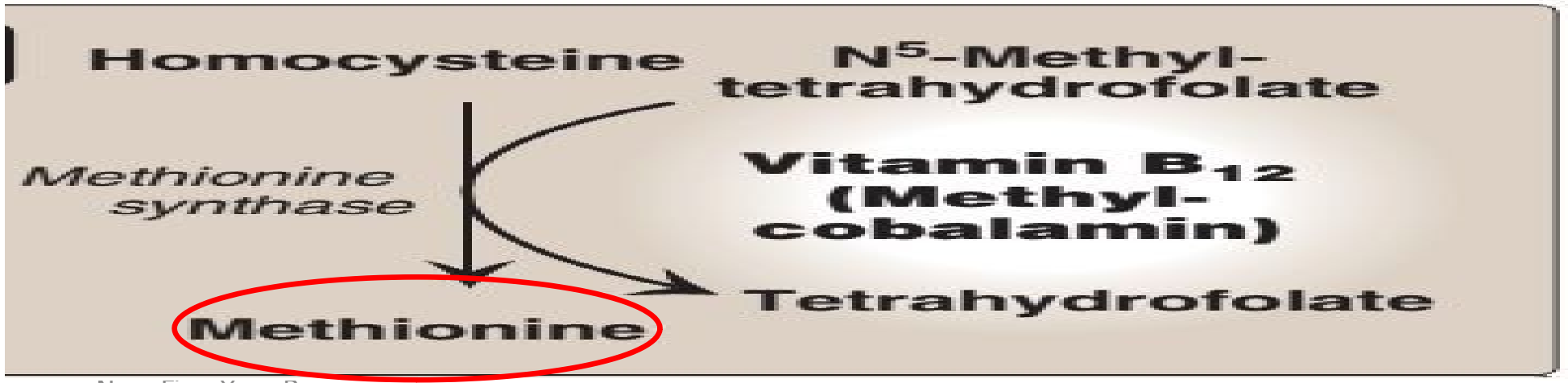
Explain on a biochemical causes NTD in folic acid deficiency?

Folate is required for the production and maintenance of new cells because it is needed to carry one carbon groups for:

- Methionine which is needed for methylation reaction through SAM
- nucleic acid synthesis: DNA synthesis and RNA synthesis

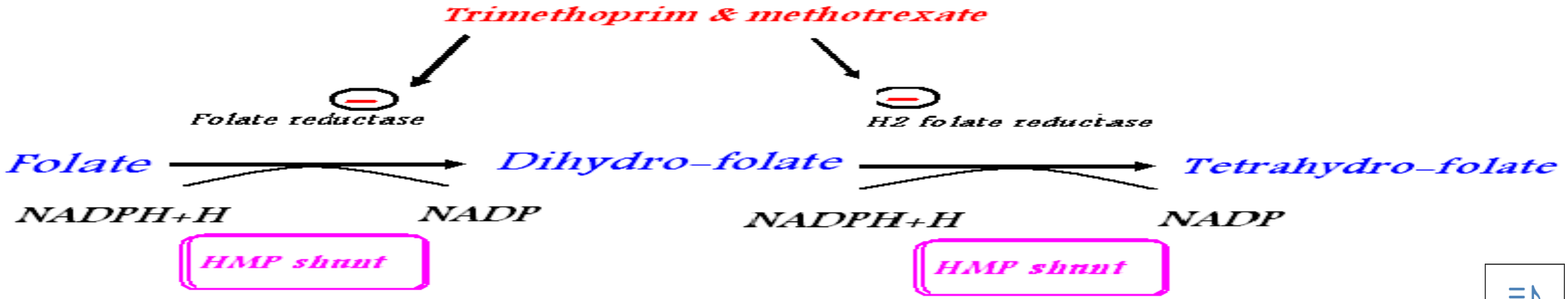
- The early human embryo may be particularly susceptible to folate deficiency due to high demand for post translational methylations of the cytoskeleton in neural cells during neural tube closure during embryogenesis



Folate Analogues

1. Methotexate & aminopetrin

- They are potent inhibitors of human dihydrofolate reductase; so prevent folate activation to THF.
- As THF used in purines & thymine synthesis, folate analogues are applied therapeutically as blockers of tumor growth (anticancer drug or chemotherapy).



2. Trimethoprim

-They are competitive inhibitor of bacterial dihydrofolate reductase.

-It inhibits DNA synthesis in bacteria.

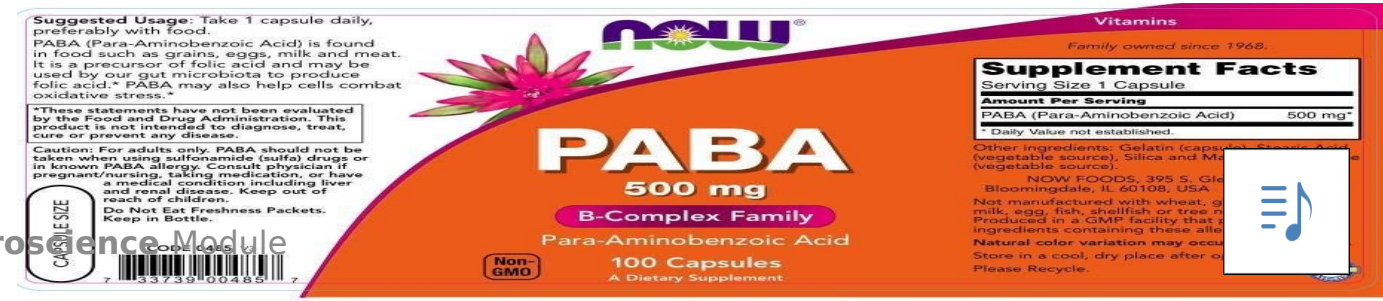
-It is applied as antibiotic.

3. Sulfonamide

-It is PABA (Para-aminobenzoic acid ;part of folic acid) analogue

-It inhibits synthesis of folic acid only in bacteria

-Used as antibiotic.


Suggested Usage: Take 1 capsule daily, preferably with food.
PABA (Para-Aminobenzoic Acid) is found in food such as grains, eggs, milk and meat. It is a precursor of folic acid and may be used by our gut microbiota to produce folic acid.* PABA may also help cells combat oxidative stress.*
*These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.
Caution: For adults only. PABA should not be taken when using sulfonamide (sulfa) drugs or in known PABA allergy. Consult physician if pregnant/nursing, taking medication, or have a medical condition including liver and renal disease. Keep out of reach of children.
Do Not Eat Freshness Packets. Keep in Bottle.
CAPSULE SIZE
now
Vitamins
Family owned since 1968.
PABA
500 mg
B-Complex Family
Para-Aminobenzoic Acid
100 Capsules
A Dietary Supplement
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Supplement Facts
Serving Size 1 Capsule
Amount Per Serving
PABA (Para-Aminobenzoic Acid) 500 mg*
* Daily Value not established.
Other ingredients: Gelatin (capsule), Silica and Magnesium Stearate (vegetable source).
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Natural color variation may occur
Store in a cool, dry place after opening.
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Folate Analogues Quiz (USMLE)

A 22-year- old woman presents to physician with frequent stool & painful tongue. Drug history demonstrates intake of methotrexate for treatment of breast cancer. Examination revealed beefy red patch in the tongue. Blood film shows megaloblastic anemia.

Which one of the following vitamin deficiency is suspected?

A. Vitamin A

B. Vitamin B12

C. Vitamin B9

D. Vitamin B1

Lecture Summary

1. The functions of folic acid
2. Clinical disorders of folic acid deficiency and NTDs
3. Folate analogues applications in Medicine

SUGGESTED TEXTBOOKS

- "Lippincott's Illustrated Reviews in Biochemistry" by P.C.Champe, R.A.Harvey and D.R.Ferrier
- "Harper's Biochemistry" by R.K.Murray, D.K.Granner, P.A. Mayes and V.W.Rodwell.
- Fundamentals of Clinical Chemistry (Tietz) Sixth
- "Textbook of Biochemistry with Clinical Correlations" by T.M.Devlin
- ***www.namrata.co- Biochemistry for medics***

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